REMARKS

Species Elections - Improper withdrawal of Claims 74-77

The Examiner has made final the requirement that the applicant elect from species 6, 7, and 8. Office Action page 3. In a response filed on October 3, 2005, Applicants elected, with traverse, Species 6 corresponding to Claim 73 (along with Claims 76-77), and identified claims 35, 47, and 62-84 as reading on this species. The Examiner now deems that Claims 74-77 are withdrawn in view of this species election. The withdrawal of Claims 74-77 is improper as Claim 73 reads on these embodiments. Single embodiments (as detailed in the Amendment and Response filed on October 3, 2005) can have all of the limitations of Claims 73-75, and the limitations of one of these claims do not preclude the limitations of the others from being found in a single embodiment - *i.e.*, they are not mutually exclusive.

Rejections

The Examiner has raised the following rejections, summarized below in the order in which they are addressed:

I. Claims 35, 47, 62-63, 65-68, 71, 73, and 78-84 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement.

II. Claims 35, 47, 62-63, 65-68, 71, 73, and 78-84 stand rejected under 35 U.S.C. §112, second paragraph as allegedly failing to particularly point out an distinctly claim the subject matter which the Applicants regard as their invention.

I. 35 U.S.C. §112, first paragraph

Claims 35, 47, 62-63, 65-68, 71, 73, and 78-84 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Examiner asserts that the limitation provided in Claim 35, step (c) and in Claim 62, wherein "said detectable signal accumulates over time" is not supported by the specification. Office Action page 4. The Examiner notes that the specification describes the accumulation of the ultimate product at an exponential rate, but asserts that this does not necessarily lead to exponential accumulation of signal. Applicants respectfully disagree. However, for business

reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original claim in one or more future applications, Applicants herein amend Claim 35 to recite "wherein said exponential accumulation of cleaved second probe over time is indicative of the presence of said target nucleic acid." Similarly, Claim 62 is amended to recite "cleaving said second cleavage structure with a cleavage agent so as to generate a cleaved probe, wherein said cleaved probe accumulates at an exponential rate over time, and wherein the accumulation of said cleaved probe at an exponential rate over time indicates the presence of said target nucleic acid in said sample." The claims depending from these claims are amended herein to be consistent with these amendments. As noted by the Examiner, the specification describes the exponential accumulation of ultimate product at, *e.g.*, page 117, last paragraph bridging to 118. Cleavage of a second probe or oligonucleotide as an "ultimate product" is supported throughout the specification, and is diagrammed, *e.g.*, in Figures 96 and 97.

The Examiner notes that Page 13, lines 6-10 and page 66, lines 3-25, do not describe detecting a detectable signal by detection of charge, as recited in Claim 66. (Office Action page 4). Charged adducts on probes and detection based on charge are discussed, *e.g.*, at page 13, lines 14-21, and at Section IV of the Description of the Invention, starting at page 73, line 15 to page 78, line 6. Examples of charged adducts are provided on page 75, lines 8-16.

Applicants have addressed each of the rejections made by the Examiner under 35 U.S.C. § 112, paragraph one. For the reasons recited above, Applicants assert that the requirements of §112, paragraph one are met and respectfully request that these rejections be removed.

II. 35 U.S.C. §112, second paragraph

Claims 35, 47, 62-63, 65-68, 71, 73, and 78-84 stand rejected under 35 U.S.C. §112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Applicants respectfully disagree.

Claim 35 and dependent claims stand rejected as vague and indefinite in view of step a), in that the Examiner asserts that it is unclear how a second cleavage structure comprising a second probe can be formed without a step that hybridizes the second probe oligonucleotide to said cleaved unpaired regions. Office Action page 5.

Applicants submit that the specification provides ample instruction on the formation of cleavage structures. For example, Figures 96 and 97 illustrate two embodiments of second

cleavage structures comprising a cleaved unpaired region and a second probe. In the embodiment shown in Figure 96, the second cleavage structure comprises a cleaved unpaired region (shown as "Cut Probe 1") from cleavage of the first cleavage structure, and a second probe (shown as "Probe 2"), as recited in Claim 35. In this embodiment, the cleaved unpaired region and the second probe **do not** hybridize to each other. Rather, they hybridize to a second target strand to form the second cleavage structure. The embodiment shown in Figure 97 provides another example of a second cleavage structure comprising a cleaved unpaired region from cleavage of the first cleavage structure, and a second probe. In this embodiment, the cleaved unpaired region and the second probe **do** hybridize to each other in the second cleavage structure. Thus, the cleaved unpaired region and the second probe MAY hybridize to each other in the second cleavage structure, but are not required to.

The second cleavage structure of the present invention is not limited by any particular relationship between the cleaved unpaired region and the second probe, so long as the second cleavage structure comprises them both. As stated in the specification at page 117, at lines 15-21, the second cleavage structures are not limited to those diagrammed in Figures 96 and 97, and "the oligonucleotide product of a primary cleavage reaction may fill the role of any of the oligonucleotides described herein, *e.g.*, it may serve as a target strand without an attached Invader oligonucleotide-like sequence, or it may serve as a stacker oligonucleotide . . ."

The Examiner asserts that it is "unclear how a second cleavage structure can be formed without a step that hybridizes the second probe oligonucleotide to said cleaved unpaired regions." The Examiner has not explained why the invention should be limited to embodiments in which the probe oligonucleotide hybridizes to the cleaved unpaired region. Applicants submit that it is not limited to this embodiment. For the reasons described above, Applicants submit that the specification clearly teaches how cleavage structures, including second cleavage structures, are formed, and further submits that the claims provide all of the details needed to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Applicants respectfully request that these rejections be removed.

Claim 62 and dependent claims stand rejected as vague and indefinite in view of step b), in that the Examiner asserts that it is unclear how a second cleavage structure comprising a probe can be formed without a step that hybridizes the probe oligonucleotide to said non-target cleaved product. Office Action page 5.

Applicants submit that the specification provides ample instruction on the formation of cleavage structures. For example, Figures 96 and 97 illustrate two embodiments of second cleavage structures comprising a non-target cleaved product and a probe oligonucleotide. In the embodiment shown in Figure 96, the second cleavage structure comprises a non-target cleaved product (shown as "Cut Probe 1") from cleavage of the first cleavage structure, and a probe oligonucleotide (shown as "Probe 2"), as recited in Claim 62. In this embodiment, the non-target cleaved product and the probe oligonucleotide **do not** hybridize to each other. Rather, they hybridize to a second target strand to form the second cleavage structure . The embodiment shown in Figure 97 provides another example of a second cleavage structure comprising a non-target cleaved product from cleavage of the first cleavage structure and a probe oligonucleotide. In this embodiment, the non-target cleaved product and the probe oligonucleotide **do** hybridize to each other in the second cleavage structure. Thus, the non-target cleaved product and the probe oligonucleotide MAY hybridize to each other in the second cleavage structure, but are not required to.

The second cleavage structure of the present invention is not limited by any particular relationship between the non-target cleaved product and the probe oligonucleotide, so long as the second cleavage structure comprises them both. As stated in the specification at page 117, at lines 15-21, the second cleavage structures are not limited to those diagrammed in Figures 96 and 97, and "the oligonucleotide product of a primary cleavage reaction may fill the role of any of the oligonucleotides described herein, *e.g.*, it may serve as a target strand without an attached Invader oligonucleotide-like sequence, or it may serve as a stacker oligonucleotide . . ."

The Examiner asserts that it is "unclear how a second cleavage structure can be formed without a step that hybridizes the probe oligonucleotide to said non-target cleaved products. The Examiner has not explained why the invention should be limited to embodiments in which the probe oligonucleotide hybridizes to the non-target cleavage product. Applicants submit that it is not limited to this embodiment. For the reasons described above, Applicants submit that the specification clearly teaches how cleavage structures, including second cleavage structures, are formed, and further submits that the claims provide all of the details needed to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Applicants respectfully request that these rejections be removed.

Claim 83 is rejected as vague and indefinite because it is clear what an "archaeal FEN-1" is. Applicants respectfully assert that the meaning of "archaeal" is clear. However, for business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original claim in one or more future applications, Applicants herein amend Claim 83 to recite "wherein said FEN-1 nuclease is a FEN-1 nuclease from an archaebacterial species." For consistency, Claim 79 is similarly amended. Support for the term "archaebacterial species" is found, *e.g.*, at page 227, lines 12-13. Applicants submit that the meaning of this term is clear and respectfully request that this rejection be removed.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all objections and rejections should be removed and Applicant's claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: March 23, 2006

Mary Ann D. Brow
Registration No. 42,363
MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105